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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,286	04/20/2001	Jacques Dumas	BAYER-14	9096

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,286	DUMAS ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 39-74* is/are pending in the application.

4a) Of the above claim(s) *26,39-49,51 and 57-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary of Action

1. The rejection of the claims 50 and 52-55 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record.

2. The rejection of the claims 50 and 52-56 under 35 USC 112, second paragraph, is not maintained in light of the amendment.

3. The provisional rejection of the claims 50 and 52-56 under the judicially created doctrine of double patenting over claims 1-11, 14-17, 23 of copending U.S. Application No. 10/361858 is maintained for the reason of record.

Status of Application

4. By Amendment filed March 03, 2005, claims 44, 45, 46 and 50 have been amended. Claims 50 and 52-56 are currently pending for prosecution on the merits.

Election/Restrictions

5. In response to the Examiner's requirement of Election/Restriction, Applicant alleges that since no prior art was found, the search and examination should be expanded to methods which employ the other species or subgenus defined in claims 51 and 59-74 as well as the disease recited in claims 57 and 58 and the subject matter which was previously elected, searched, examined and allowed in this prior to filing the RCE.

This argument is not found persuasive. Since this instant application is not ready for the allowance, there is no need for the Examiner to consider additional species at this time.

With respect to the Applicant's request to rejoin the product claims that were previously elected, searched, examined and indicated-allowability by the independent Examiner, William

Jarvis, into the instantly elected method claims, the Examiner determines that the requirement between the product and process of use is still deemed proper. Since the full scope of the elected subject matter was not completely searched by the previous Examiner, there would be significant burden for the instant Examiner to search the entire groups. Furthermore, the search of the entire groups in the non-patent literature (a significant part of a thorough examination) would be burdensome. Therefore. The requirement is still deemed proper, and made Final.

Priority

6. In absence of Applicant's showing evidence to support the elected species in the earliest priority application, the Examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the disclosure of the application relied upon fails to convey to the artisan that the inventor has possession at that time of the later claimed subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 50 and 52-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (i.e., rheumatoid arthritis, osteoarthritis and septic arthritis), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host", "the treatment of a disease other than cancer" with "a compound of Formula I ". The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The claimed invention is directed to a method for the therapeutic treatment of all types of diseases mediated by p38 including cancer (claims 50, 52-54) or all types of diseases mediated by p38 other than cancer (claim 55), comprising administering said compounds represented by the Formula I.

The nature of the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations and subsequently administering the instant composition. The instant specification discloses over 100 different types of diseases that are mediated by p38.

There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated thru p38 or (ii) all types of diseases other than cancer that are mediated thru p38. Since this assertion is contrary to what is known in medicine,

proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacotherapeutics.

With respect to the treatment of "disease mediated by p38 within a host" in claims 50 and 52-54, the scope of instant claims encompasses various diseases including cancer. For instance, in cancer therapy art, it is recognized that different types of cancers affect different organs and have different method of growth and harm the body. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or cancers mediated by p38.

With respect to the treatment of "a disease other than cancer", as stated above, the scope of the instant claims encompasses over 100 different types of diseases that may be related to p38 pathway mechanism. Although the specification links the p38 pathway signaling to numerous diseases, there is no proof or any competent evidence provided in the state art that inhibition of p38 leads to the effective treatment of the claimed disease conditions.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of

unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The instant claims embrace the therapeutic treatment of all diseases that are potentially mediated by p38 (claims 50, 52-54) and except cancers (claim 55). The breadth of the claims is further exacerbated by the instantly claimed plethora of compounds that are represented by compound of Formula I.

The specification discloses that inhibition of p38 inhibits both cytokine production (eg., TNFα, IL-1, Il-6, IL-8) and proteolytic enzyme production (e.g., MMP-1, MMP-3). See page 2, lines 10-13. In addition, the specification discloses over 100 different types of diseases that are related to excessive levels of TNFα, excess or undesired matrix-destroying metalloprotease (MMP) activity or an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases. See page 2, line 14 thru page 5, line 17.

The specification discloses the p38 inhibitory activity of the compounds in vitro assay (bottom of page 74 thru page 75) and the activity of the claimed inhibitors of p38 in murine lipopolysaccharide (LPS) model (in vivo) of TNFα production (page 75).

As stated above, the instant invention correlates the involvement of p38 pathway mechanism in biosynthesis of various cytokines and proteolytic enzymes and their potential utility in the treatment of numerous diseases that are known to be mediated by one or more of the cytokines and proteolytic enzymes. However, the specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of all of the claimed disease conditions that are mediated by p38 without undue amount of experimentation.

Since the efficacy of the claimed compounds in treating complex diseases condition may have unrelated manifestation mentioned above or cancers due to p38 cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 50 and 52-56 are rejected under the judicially created doctrine of double patenting over claims 1-11, 14-17, 23 of copending U.S. Application No. 10/361858.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of referenced species of the genus or subgenus of the formula overlaps with the instantly claimed invention. Since the reference teaches the species of the genus or subgenus as having similar properties of the claimed invention, the reference makes obvious the claimed invention.

In looking in continuity data, it is noted that applicant has numerous issued patent and pending application encompassing the same or similar subject matter of the instant application. Applicant review all subject matter considered same or similar, and submit the proper Terminal Disclaimer(s). For example, 09/776935, 10/086417 to be same or similar subject matter(s).

Response to Arguments

9. Applicant's arguments filed March 03, 2005 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that the specification provides more than it needs to, e.g., in vitro p38 kinase assays (and IC50 data) and in vivo assays. Applicant alleges that one of ordinary skill in the art by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating various cancers.

This argument is not found persuasive. Although the instant application ties all of the seemingly unrelated more than 100 known diseases as to a single underlying mechanism, the art recognizes the pathophysiology of diseases encompassed by the instant invention involves multitude of factors. For instance, in cancer therapy art, it is recognized that different types of cancers affect different organs and have different method of growth and harm the body. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to

get an agent to be effective against all cancers or cancers mediated by p38. Similarly, the skilled artisan would have not predicted that the administration of said compounds having p38 kinase inhibiting activity would be capable of treating the seemingly unrelated more than 100 different types of disease conditions including rheumatoid arthritis, osteoarthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis, aneurismal aortic, birth control, dystrophobic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP acitivity, tempero mandibular joint disease or demyelating disease of the nervous system, etc...

Applicant's argument in the response takes the position that the claims in US application No. 10/361,858 are directed to distinct methods target the VEGF-induced signal transduction pathway and not p38. Applicant states that although Applicant acknowledge the compounds employed in teach of these methods significantly overlap, however, the dame compound can be used in patentably distinct methods.

This argument is not found persuasive. Although the underlying mechanism involved in the treatment of claimed condition is different between the instant application and the copending application, both applications are drawn to the treatment of same condition (see for example claim 56 of the instant application and claims 15-17). Since the referenced teaching in administering the same compounds inherently possessing therapeutic effects for the same ultimate purpose as disclosed by the instant application anticipates the instant invention even absent explicit recitations of the underlying pharmacological mechanism. Therefore, the copending application makes obvious the instant invention.

It is noted that in absence of approved Terminal Disclaimer at this time, the Examiner maintains the provisional rejection of the claims 50 and 52-56 under the judicially created doctrine of double patenting over claims 1-11, 14-17, 23 of copending U.S. Application No. 10/361858.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. No Claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
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AU 1614

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